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2017-03

Tuomikoski , P & Savolainen-Peltonen , H 2017 , ' Vasomotor symptoms and metabolic syndrome ' , Maturitas , vol. 97 , pp. 61-65 . https://doi.org/10.1016/j.maturitas.2016.12.010

http://hdl.handle.net/10138/236409
https://doi.org/10.1016/j.maturitas.2016.12.010

publishedVersion

Maturitas 97 (2017) 61–65

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Vasomotor symptoms and metabolic syndrome

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ARTICLE INFO

Article history:
Received 3 December 2016
Accepted 16 December 2016

Keywords:
Hot flushes
Sympathetic overactivity
Menopause
Metabolic syndrome
Blood pressure
Insulin resistance
Obesity
Adipokines

ABSTRACT

A vast majority of menopausal women suffer from vasomotor symptoms, such as hot flushes and night sweats, the mean duration of which may be up to 7–10 years. In addition to a decreased quality of life, vasomotor symptoms may have an impact on overall health. Vasomotor symptoms are associated with overactivity of the sympathetic nervous system, and sympathetic overdrive in turn is associated with metabolic syndrome, which is a known risk factor for cardiovascular disease. Menopausal hot flushes have a complex relationship to different features of the metabolic syndrome and not all data point towards an association between vasomotor symptoms and metabolic syndrome. Thus, it is still unclear whether vasomotor symptoms are an independent risk factor for metabolic syndrome. Research in this area is constantly evolving and we present here the most recent data on the possible association between menopausal vasomotor symptoms and the metabolic syndrome.

Contents

1. Introduction

Up to 80% of menopausal women suffer from vasomotor symptoms. Follow-up studies [1–3] have shown that the mean duration of vasomotor symptoms is longer than previously thought, up to 7–10 years. Despite the fact that vasomotor symptoms are very common, the precise etiopathology behind them is still unclear. Vasomotor symptoms are a profound physiological reaction to hypoestrogenism due to the decline in ovarian function and they are also associated with an overactivity of the sympathetic nervous system [4]. The decrease in endogenous estradiol, either through surgical or natural menopause, and an elevated central sympathetic tone, mediated through alpha-2 adrenergic receptors, are associated with a narrowed thermoneutral zone in the thermoregulatory center in the brain. These changes in temperature regulation in symptomatic women cause small increases in core body temperature to trigger vasomotor symptoms, such as hot flushes and night sweats [4].

An abundance of evidence link chronic activation of the sympathetic nervous system and metabolic disturbances [5]. Elevated

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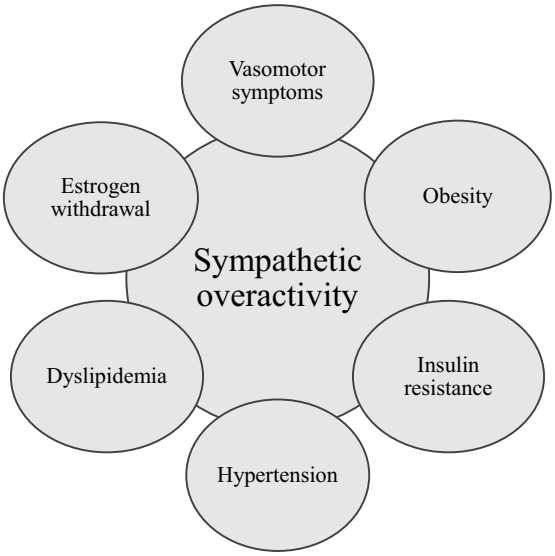
http://dx.doi.org/10.1016/j.maturitas.2016.12.010
0378-5122/



Complex interplay between vasomotor symptoms, estrogen withdrawal and different features of the metabolic

Fig. 1. Complex interplay between vasomotor symptoms, estrogen withdrawal and different features of the metabolic syndrome. Based on [4,5,8].

sympathetic tone may result in altered vascular function [6], changes in blood pressure [7] and lipids [8], and development of insulin resistance [5]. The metabolic syndrome (MetS) is a cluster of closely related risk factors for cardiovascular disease and type 2 diabetes. These include increased blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), hyperglycemia and central obesity [9]. Prothrombotic and proinflammatory states and insulin resistance are also related to MetS. The prevalence of MetS is increasing rapidly in line with the growing obesity epidemic [10]. Although weight gain at midlife is not primarily influenced by menopause [11], the hormonal changes are associated with increased total and abdominal fat [12–14]. These changes in the body composition are a risk factor for insulin resistance and the progression of type 2 diabetes. Furthermore, abdominal obesity may be related to an adverse lipid profile.

Vasomotor symptoms and MetS share a common nominator, sympathetic overactivity (Fig. 1). Thus, menopausal women with vasomotor symptoms could well be at risk for MetS. On the other hand, MetS may also exacerbate sympathetic overdrive [15] and perhaps worsen vasomotor symptoms. Obesity is a mediator both in vasomotor symptoms and MetS and its' interactions and the endocrine functions of the adipose tissue are targets for an abundance of research. In this review we present the most recent findings on vasomotor symptoms and the MetS, especially with regard to the persistence or severity of hot flushes and the role of the adipose tissue.

2. Vasomotor symptoms and blood pressure

Menopause-associated alterations in the function of the autonomic nervous system may contribute to the increase in blood pressure [7]. According to a recent systematic review with pooled analysis (12 studies, 19 667 women) published in this Journal [16] in 2015, systolic blood pressure tended to be higher in women with hot flushes (mean difference 1.95 mmHg, 95% CI 0.27-3.63) or night sweats (mean difference 1.33 mmHg, 95% CI, 0.63-2.03). For diastolic blood pressure, only night sweats were associated with a higher mean (mean difference 0.55 mmHg (95% CI, 0.19–0.91), when compared with women with no symptoms. Hot flushes *per se* did not confer an increased odds for hypertension, but night sweats were associated with a higher odds of hypertension compared to those without (OR 1.17, 95% CI: 1.04–1.31, one study) [16].

Not all cross-sectional data are uniform on the detrimental effects of vasomotor symptoms and blood pressure. One study actually found that women with most frequent vasomotor symptoms during 24 h had lower systolic blood pressure [17]. Also data on no association between vasomotor symptoms and blood pressure exist e.g. [18]. Looking at different menopausal stages, the effect of vasomotor symptoms on blood pressure seems mixed. In a cross-sectional study on 590 perimenopausal women there was no association between vasomotor symptoms and blood pressure [19]. In another study both systolic and diastolic blood pressures were significantly higher in women with vasomotor symptoms either <10 years or ≥10 years postmenopausal, when compared with women without symptoms [20]. Of note, women in both studies [19,20] showing increased blood pressure with vasomotor symptoms were overweight with a mean BMI between 26 and 29 kg/m^2. On the contrary, women in studies [17,18] showing lack of association were lean with a mean BMI ≤25 kg/m^2.

As vasomotor symptoms tend to last for several years, the possible impact on different markers for cardiovascular disease may be best studied in a longitudinal setting. One of the recent reports from the SWAN study elaborate on the association between vasomotor symptoms and blood pressure [21]. In this study data on vasomotor symptoms and blood pressure was collected at each annual study visit. The study included 2839 women and mean follow-up was 8.2 years. Women with ≥6 days with vasomotor symptoms during the preceding two weeks had greater increases in diastolic blood pressure over time than did asymptomatic women, or those with less symptoms. Also the risk of developing pre-hypertension or hypertension during follow-up was increased among these women (hazard ratio of 1.39, 95% CI; 1.09–1.79) even after adjustment for multiple covariates [21].

It seems that vasomotor symptoms may be associated with increased blood pressure. However, obesity may be a factor that modulates this effect. More data are also needed regarding the impact of the severity of vasomotor symptoms on blood pressure.

3. Vasomotor symptoms and lipids

In accordance with blood pressure, vasomotor symptoms starting already in premenopause may not associate with lipids, glucose levels or insulin sensitivity [22]. This was detected in a Canadian 4-year follow-up study (n = 80) where vasomotor symptoms were

assessed with mailed questionnaires with 3 month intervals and blood samples were taken annually. At the end of the follow-up the study group consisted of only 37 women of whom 6 were asymptomatic and 31 symptomatic. Due to the small numbers and the fact that 88% of the women were symptomatic at some point, it may be impossible to determine for certain the lack of associations [22]. A follow-up time of only four years may also be too short to distinguish the impact of vasomotor symptoms on markers of metabolic health. Indeed, in the SWAN study the presence and frequency of vasomotor symptoms after 8 years was associated with higher lipid and lipoprotein levels [23]. Overall, quality data on vasomotor symptoms and lipids seems scarce. In the pooled analysis by Franco et al. [16] data on hot flushes and lipids included consisted of only two studies. A larger number of studies were analyzed for night sweats, and the meta-analysis showed that night sweats were associated with significantly increased levels of total cholesterol (0.17 mmol/L, 95%CI 0.03–0.31) and LDL-cholesterol (mean difference: 0.07 mmol/L, 95% CI 0.01–0.13) [16].

4. Vasomotor symptoms and insulin resistance

Estrogen deficiency has been shown to alter insulin sensitivity and predispose to diabetes in animal models [24]. A recent systematic review on vasomotor symptoms and metabolic health in peri- and postmenopausal women concluded that many studies on vasomotor symptoms and metabolic health were of too low quality and high heterogenicity to make definite conclusions [25]. In the SWAN study cohort of 3075 women with 8 years of follow up, hot flushes were related to a higher HOMA-index, a measure for insulin resistance [26]. This finding persisted after adjusting for levels of estradiol and follicle-stimulating hormone. Similar associations were also observed for fasting glucose level. These findings were not supported by cross-sectional studies [27,28] where fasting glucose and HOMA-index did not differ according to the presence of vasomotor symptoms [28] or according to the number or severity of hot flushes [27].

Vasomotor symptoms and insulin resistance were studied recently in 1547 Korean postmenopausal women [29]. In this cross-sectional study, the severity of vasomotor symptoms was assessed by the Menopausal rating scale, and 57% of the women reported vasomotor symptoms to some degree. The HOMA-index increased with the increasing severity of the symptoms (none, mild, moderate, severe). Although all study participants were normal weight, the BMI was significantly higher in women with severe hot flushes compared to woman without hot flushes.

Mechanisms linking hot flushes with insulin resistance remain unknown. Vasomotor symptoms and insulin resistance share common risk factors, especially elevated BMI, and there are conflicting data on whether BMI explains the positive association between vasomotor symptoms and insulin resistance [26,29–31]. Increased sympathetic nerve activity has been linked to decreased glucose uptake and insulin resistance as well [32]. However, the complex interactions between sympathetic nervous system, metabolism, obesity, hyperinsulinemia, and insulin resistance make it difficult to define, which is the primary factor leading to metabolic dysfunction.

5. Vasomotor symptoms and obesity

Adipose tissue is an active endocrine organ, it synthesizes steroid hormones and several bioactive mediators, called adipokines. Adipokines are able to regulate metabolism and other body functions, such as immunity, insulin resistance, blood pressure, and lipid metabolism [33]. Central obesity is characterized with chronic low-grade inflammation of adipose tissue. This results in impaired regulation of the normal adipokine secretion, endothelial dysfunction and metabolic dysregulation [33].

Both epidemiologic and longitudinal studies have linked obesity with hot flushes [34–37]. This is contradictory to the traditional assumption that adiposity protects from hot flushes through peripheral aromatization of androgens into estrogens. In the SWAN longitudinal study, higher odds of hot flushes in pre- and early perimenopause was related to an adverse adipokine profile (higher leptin, lower adiponectin level). Increased level of macrophage chemoattractant protein 1 was also associated with higher odds of night sweats [37]. Several smaller studies support the association between hot flushes and impaired adipokine secretion [38–40].

In postmenopausal women screened for MetS, higher levels of adiposin, leptin, resistin, insulin and HOMA-IR values and lower adiponectin levels were associated with MetS [41]. These differences were mainly observed among women with abdominal obesity.

The mechanisms behind the association between adipokines and hot flushes are not clear, but adipokines have been shown to influence the central nervous system, the body temperature [42,43] as well as sympathetic nerve activity [32]. In recent years, the regulation of vascular tone and endothelial function by adipokines released from the perivascular adipose tissue has also raised interest [44]. The substances could in theory modulate vasomotor function.

Thus, there is some support for the idea that adipokines may be one mechanism linking increased adiposity, metabolic disturbances and hot flushes in postmenopausal women.

6. Impact of severity or timing of vasomotor symptoms

The field of menopause research is evolving and more research is directed towards the impact of vasomotor symptoms. As regards cardiovascular outcomes, a Finnish study found no signs of an adverse cardiovascular risk profile in recently postmenopausal women with either mild, moderate or severe vasomotor symptoms [45]. Similarly, in the KEEPS trial [46], hot flushes or night sweats were not associated with either the amount of coronary calcium or intima-media thickness. Both studies included only lean women and obesity may indeed be a factor that modifies the risk profile associated with vasomotor symptoms. Interestingly, long-lasting vasomotor symptoms that begin already in the early menopausal years are associated with a higher intima-media thickness when compared with women who traverse through menopause with a low frequency of hot flushes [47]. This indicates that the longevity of vasomotor symptoms may be of more significance than just the presence of hot flushes.

7. Further research

More research on vasomotor symptoms and subsequent metabolic and cardiovascular risk is needed. Majority of the data available are cross-sectional and information on vasomotor symptoms is gathered through diaries or questionnaires, which are a subject of recall bias [48]. Moreover, all vasomotor symptoms are not subjectively observed by the women [49]. Thus, future studies need long-term follow-up and also to utilize objective measurement of vasomotor symptoms.

The guidelines on postmenopausal hormone therapy use have recommended the treatment to be directed to moderate to severe symptoms and to be as short in duration as possible. From a cardiovascular point of view, if vasomotor symptoms indeed are a risk factor for metabolic disease, should also mild symptoms be treated? Furthermore, due to the longevity of vasomotor symptoms, should longer treatments be encouraged after all?

8. Summary

Menopausal vasomotor symptoms may be associated with an increased risk of MetS. More data are needed on the effect of prospectively and objectively recorded vasomotor symptoms on metabolic syndrome and other cardiovascular risk factors. Moreover, physicians need to be observant when taking care of women with long-lasting hot flushes and remember to screen them also at a later age for underlying MetS or cardiovascular disease.

Contributors

PT and HS-P contributed equally to designing the paper, gathering, analyzing and interpreting the data and writing the paper.

Funding

No funding was sought or received for writing this review.

Conflict of interest

PT has been a speaker and received consulting fees from Mylan, Novo Nordisk and Orion, and received funding for congress trips from Mylan.

HS-P has been a speaker for Mylan and received funding for congress trips from Mylan and Finox Biotech.

Provenance and peer review

This article has undergone peer review.

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